



<b>CLINICAL DATA REVIEW</b>  <ul style="list-style-type: none"> <li>• <b>Antiepileptics</b></li> </ul>	Francine Goodman, PharmD. BCPS	Dr. Goodman attended via conference call and presented the Oregon Evidence-Based Practice Center's report comparing the antiepileptics drug class. This report was finalized in November of 2004. The Committee accessed and reviewed a copy of the report prior to the meeting.
<b>PUBLIC COMMENT PERIOD</b>	W. Terry Gipson, MD	Three people were listed to speak during the public comment period. Public comment was received from the following: <ul style="list-style-type: none"> <li>• Norm Brown, GlaxoSmithKline – Antiepileptics</li> <li>• Jeffery Berlant, M.D. – Antiepileptics</li> <li>• Sneha Patel, Pharm.D., Wyeth – ACE Inhibitors</li> </ul>
<b>COMMITTEE DISCUSSION AND CLINICAL CONCLUSIONS FOR SELECTED THERAPEUTIC CLASSES</b>	W. Terry Gipson, MD	<u>ACE Inhibitors</u> The Committee determined that all the agents are equivalent, and there are no changes relative to efficacy due to the updated data.  <u>Antiepileptics</u> The Committee determined that agents in this class have uniqueness in uses, efficacy, safety profiles, and drug specific advantages.
<b>MENTAL HEALTH PHARMACY MANAGEMENT INITIATIVE PROGRAM PLAN</b>  <ul style="list-style-type: none"> <li>• <b>Comprehensive NeuroScience Inc. Program Overview</b></li> <li>• <b>Selected Case Reviews</b></li> </ul>	W. Terry Gipson, MD  Bruce Goreman	Mr. Goreman presented to the Committee information about CNS, the company, goals, identified quality indicators, and program plan for mental health mediations.
<b>DUR COX II PRESENTATION</b> <ul style="list-style-type: none"> <li>• <b>Outcomes Study</b></li> </ul>	Heather Brandt, PharmD	Dr. Brandt presented data on the cost, utilization, and prior authorization of COX II agents. The results showed a cost savings as a result of the PA process however noted that additional information would be difficult to gather as a result of Vioxx® withdrawal from the market.
<b>PUBLIC MEETING ADJOURNED</b>	W. Terry Gipson, MD	The next classes of agents to be reviewed by the Pharmacy and Therapeutics Committee on March 18, 2005 are: Atypical Antipsychotics, Inhaled Corticosteroids and a re-review of Calcium Channel Blockers.  Dr Gipson adjourned the public portion of the meeting.
<b>SUPPLEMENTAL REBATE INFORMATION (CLOSED TO PUBLIC)</b>	Randy May, Medicaid Deputy Administrator	Mary Wheatley presented supplemental rebate information to the Committee members for their review and discussion. This review and discussion were closed to the public.
<b>COMMITTEE FINAL RECOMMENDATION FOR THERAPEUTIC CLASSES</b>	W. Terry Gipson, MD	<u>ACE Inhibitors</u> The Committee recommends Captopril, Enalapril, Lisinopril and Ramipril (Altace®) as preferred agents. All other agents will require prior authorization.  <u>Antiepileptics</u> Due to the uniqueness, efficacy, safety profiles, and the drug specific advantages of the agents in this class no preferred agent will be designated. The Committee recommends all agents all agents be available with limitations on the following six (6) agents. <ul style="list-style-type: none"> <li>• Keppra® for Seizures only</li> <li>• Lamictal® for Seizures and Bi-polar disorder</li> </ul>

		<ul style="list-style-type: none"><li>• Neurontin® (Gabapentin) for Seizures and Neuropathic Pain</li><li>• Topamax® for Seizures and Migraines</li><li>• Trileptal® for Seizures and Bi-polar disorder</li><li>• Zonegran® for Seizures only</li></ul> <p>All other indications for these six agents will require prior authorization.</p>
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**Pharmacy and Therapeutics Committee**  
**Public Comment**  
**January 21, 2005**

Norm Brown, GlaxoSmithKline – Antiepileptics

Mr. Brown: Good Morning, Chairman and P&T Members. I would like to thank you for this time you have given me to speak. The OHSUEPC Report is important for what it does and doesn't say about antiepileptics and Bipolar disorder. Bipolar is a chronic disease requiring long term management, frequently with more than one drug to control mood episodes. Depressive symptoms are three and one half times more frequent than manic episodes but the treatment of manic has been given more attention. Drug efficacy and safety are paramount and long term adherence to therapy is critical. The report emphasizes a lack of good quality trials and yet suggests that the efficacy is similar among Lithium, Valproate, and Carbamazepin and Lamictal. The report noted that site fact profiles differs significantly among the drugs, an important finding since side effects can adversely impact long term maintenance. However, the report did not examine difference between drugs with respect to compliance or long term adherence. Recently Lamictal has been shown to be affective and well tolerated in two eighteen month landmark clinical trials. Compared with Lithium and placebo in bipolar I patients. These trials resulted in Lamictal being first and thus far the only second generation antiepileptic drug with FDA indication for maintenance therapy in Bipolar, including manic, hypo manic mixed states and depressive phases. Results were more robust for depression which is the most common phase of the disorder. No other antiepileptic drug has the breadth and depth of data in long term bipolar maintenance. The report suggests that the results comparing Lamictal and Lithium were confounded by the use of open label Lamictal during stabilization prior to randomization. These studies were prospectively designed to be combined and they were used as a partial enrichment design commonly used for modern maintenance studies. Patients were required to complete only one week of mono therapy with Lamictal after discontinuing other medications, which means the randomization process was not highly enriched. EPC report mentions difficulties comparing Lithium and Lamictal in these studies. However, these studies were never meant to compare the two drugs. They were not powered to do so either. Lithium has been included as an active control to validate the study design not as a comparator to Lamictal. Together these two landmark trials represent the largest single data base in Bipolar disorder as well as the largest data base of efficacy of Lithium thus far. In addition the efficacy and safety Lamictal offers many real world advantages are offered also. Pregnancy category C as opposed to Carbamazepin and Valproate which are category D. Also no serum level monitoring is required with Lamictal. Weight gain and adverse cognitive effects are not commonly seen. Rates of mania as an adverse event were similar to placebo and Lamictal and can be initiated at anytime. Its pharmacokinetic properties are well defined and dosing regimens are well established for either monotherapy or in combination with other drugs. Chronic long term nature Bipolar disorder requires both phases of the illness to be treated with long term without exacerbating either phase. Treatments that offer opportunity for long term maintenance are critical. Lamictal's ability to delay reoccurrence of mood episodes is well established especially in depression side. The EPC Report mentions rash, as for reason for discontinuation yet recent analysis have shown the risk of serious rash is no greater than with many other drugs. Risk factors for rash are well defined and include young age, use with Depicote, and most importantly exceeding the recommended initial dose or escalating to fast. Lamictal has no indication for neuropathic pain and the EPC Report acknowledged the lack of head to head trials. The report focused primarily on placebo controlled trials of Lamictal for the treatment of peripheral neuropathy associated with HIV, mixed neuropathic pain syndromes and central post stroke pain. It is significant that one of the double blind placebo controlled studies Lamictal attenuated painful diabetic neuropathy and had superior analgesic effects as compared to placebo. The report also discusses the opposing results of the subgroup analysis of the two placebo controlled trials evaluating Lamictal for the treatment of patients with HIV associated peripheral neuropathy. Over the first trial was a pivotal study with a small sample size as well as considerable drop out rate and both

studies were conducted by the same investigator. Given its effectiveness and favorable tolerability profile Lamictal is an extremely valuable tool especially in managing bipolar long term. Therefore, Lamictal is a very desirable evidence based choice for your formulary decision. Thank you.

CommitteeCommitt Thank you, Norm.

Committee. Brown: Any questions?

Committeemmittee: I'm sorry, I missed the introduction. I'm not sure who you are and what your background is.

Mr. Brown: I'm Norm Brown and I'm with Glyxal, Smith, Kline.

Committee: So, how come you guys have a black box warning for rash?

Mr. Brown: Why?

Committee: Because nobody else does. There's other rashes...

Committee. Brown: Oh yeah, there's. Excuse me, nobody else meaning the AED's? Well, there's a black box warning as far as rash now. The reason is when we first came out with the drug there were different dosing recommendations and that is why we got, we had to put the black box in when we relooked at pediatric patients that's were it was one in a hundred. So,

Committee The over all incidences in adults was one in three hundred. And now that more and more patients are treated with it for Bipolar we will probably go back and do a reevaluation. I'll let Dr. Berlant, he is going to speak today maybe address some of the rash data too.

Committeemmittee: I had just seen a figure I thought about eight per thousand, which would be considerably higher than three in one hundred.

Mr. Brown: In adults.

Committee: We're talking rash, er?

Mr. Brown: Rash is 10%

Committee: Not toxic epidural necroma.

Mr. Brown: Right, just general rash is 10% of package insert and then serious rash, Steven Johnsten or TEAIR in adults is one in three hundred.

Committee: That's a life threatening condition.

Committee: That is a horrible scalded skin, just like you can't believe.

Mr. Brown: It is, and so is Bipolar. More people commit suicide...

Committee: Well I think, maybe, maybe, but more people die more acutely and in much more pain.

Mr. Brown: It's a terrible rash, you're right.

Committee: Thank you very much Norm.

Jeffery Berlant, MD – Antiepileptics

Dr. Berlant:

Good Morning. Thank you for the opportunity to speak before you. My name is Jeffery Berlant, I am a physician and boarded in psychiatry as well as internal medicine. I'm in full time practice of adult psychiatry here in Boise, Idaho and I am here completely in an individual capacity. Before I forget it, I guess just to give a comment about the Lamictal rash issue, before I give my comments, although patients will get rashes it is important to evaluate them properly when the medication is prescribed according the recommended guidelines the Germany studies, which have been done with the dosing protocol in several tens of thousands of patients find a risk of Stevens Johnstons syndrome a valid one in six thousand, one in five thousand, essentially as a practitioner I would have to treat 200 patients a year for 30 years before I would see a case of Stevens Johnstons syndrome. The other cases of TEM or rare hypersensitivity reaction are far more rare than that. So this is, although it is a complication to be aware of and to learn how to prevent, it actually is far less of a problem than [unintelligible] of Lithium, the deaths that have seen black box warning with Valproic acid, or Carbamazapin actually the risk of Stevens Johnstons syndrome is comparable with Carbamazapin, Dylanton, and the use of Sulvonamide antibiotics, which active sulvonamides are higher risk than the use of Lamictal. And those medications used to be dispensed almost as though they were Pez candies to patients with urinary tract infections. And that was not feared, perhaps it should have been.

I would like to address the other issue because I'm struggling a lot with the issue of the conflicts potentially between good clinical practice and the introduction of themes of evidence based medicine or psychiatry into these discussions in policy decisions. And it is very important because Bipolar disorder of all the psychiatric disorders and many medical disorders is a very high prevalence disorder that also is associated with high utilization and high potential negative patient outcomes if it is not handled well. As least 1% of the general population has Bipolar I disorder the most severe form, another 1% or more have Bipolar II disorder and anywhere from 3 to 6.5% more may have other bipolar spectrum disorder. So we're looking at potential as much as 10% of the population may have this condition and in the Medicaid population possibly even higher because you have sicker people concentrated in that group. Most of the time with the illness is spent depressed. Although mania has been a high point because it can be spectacular when it occurs. Depression is where the social and medical burden lies with this illness. And treatments that focus on that come at a premium. Depression contributes to most of the disability and workplace, family and social function. It can be very hard to treat. Overall follow up studies suggest that 60% of patients intensively followed over a year remain moderately to severely ill with Bipolar disorder. The consequences can be grave in terms of public health affects. About 25% of Bipolar I disorder patients attempt suicide, about 10% complete suicide. Although the studies vary a bit there. The suicide risk is greatest with depression, next with what are called the mixed states combined mania and depression and lowest during mania, but not absence. Utilization of health services is very high. We know already patients who are depressed tend to use medical and psychiatric services more than the general population. But with Bipolar depression utilization of both is about 4 times higher than it is with non-Bipolar depressed patients. So this is a high consequence population. The illness starts earlier in life, the depressions tend to be more severe than non-Bipolar disorder and there is a greater use of hospital services for this group. In fact, if you look at some of the costs per lifetime for patients, one of the highest groups is identifiable is the chronic non responsive Bipolar patient who in studies that were done in 1998 dollars were found to average \$624,000.00 lifetime per person. So these are high risk patients that need to be targeted. Now from a clinician's point of view our treatments are much better now than they have been in the past. Twenty-five years ago we had Lithium; the brave ones were using Carbamazapin. We didn't have too much else, anti-psychotic medicines in some cases. We now have many different anti-convalescent agents, we have the atypical neurleptics and we have other new emerging treatments, many of them appearing over the last five to ten years. In some cases less. Now, I appreciate the general need that this committee faces, to take on an awesome task. And that is to try to find some way to contain costs yet obtain maximum value for the dollars that are invested into care. And that is an extremely important charge they have. But I doubt that a study

or an assessment like the Dirk study, which this committee, I believe has, is going to be very helpful to you. In fact, it may subvert your purpose of containing cost and obtain value. Now, let me give you some reasons why I think that. First of all, that particular study as I read it comes across as being very clinically unsophisticated. It may be I do notice that none of the principle authors are physicians or psychiatrists; they may not even be clinicians. And there are consequences, some distortions, introduced by the way they proceed. Let me tell you what I mean. For instance, one of the key things and I am only talking about Bipolar disorder, is to ask, Ok, which anti-convulsants are better for treating Bipolar disorder? This about as pointless as asking which cancer chemotherapeutic agents are better for treating cancer, or which antibiotics are better for treating fever. That's not a clinical meaningful kind of question. We want to know what kind of cancer; we want to know what kind of infection is causing fever. You have to get more specific. What we do know as we look at the literature, and there is some very good control data, when it comes to classic meaning of, without any coincident depressive symptoms, very strong evidence Lithium is better than Faproic acid or Depreco. When we look at mixed mania or mixed states where there is depression and mania together, very strong evidence that Lithium is no better than placebo or Faproic acid and Depreco is superior. If we look at depression the anti-convalescent that seems to shine is Lamotragene or Lamigdal. There is certainly the long term maintenance studies that Norman Brown had mentioned that have been done that provide very strong evidence for protective affect against the recurrence of certainly depression and maybe even to some extent, mania in Bipolar I patients maintained with Lamictal. In clinical practice we find the use of Lamotragene extremely useful in Bipolar II disorder patients, the ones who don't have flagrant mania who have predominantly depression. And these, even monotherapy that has been a very useful approach even though the data lags because of some of the methodological difficulty of defining who is Bipolar II for research purposes. Now, what else do we know? There is good double blind placebo controlled evidence suggesting Lamotragene is affective for the treatment of acute bipolar depression. In fact the clinical affect size is the same as it is for the combination of Alazapin and Faloxatin a combination that was just approved this past year by the Food and Drug Administration for the acute treatment of bipolar treatment. In fact it is the only FDA approved treatment for that. That's a very expensive treatment with unknown safety issues. Where as we have Lamotragene which hasn't supplied enough data to get and FDA approval. But we know it's good for maintenance, we have evidence that is clinically, it also seems to be selling and convincing that this kind of medication works with this very dominant form of, now we also know that Lamotragene is the only issue that has been approved, has been shown, better than a placebo for any rapid cycling bipolar conditions, specifically Bipolar II rapid cycling. It doesn't work in Bipolar I's and the data for Bipolar I's in prevention of mood swings is diluted actually because almost 30% of those patients had rapid cycling Bipolar I disorder. So the differences might have been different if they excluded the patients that we believe don't respond anyway. So where am I going with all of this? What's clinical reality and what do we have from these kinds of findings, how do we put them together? The clinical reality is that bipolar disorder is probably due to several different biological disturbances. It's heterogeneous and different folks need different medication to get approval. Now, although there are some Bipolar II patients who may do very well with mono therapy, what we see in the reality is Bipolar I patients the vast major seem to need more than one mood stabilizing drug to get control of their illness for the long term. Other academic centers like UCLA, the estimates are about 70% of patients, yet the trials that you see and which are documented are all for mono therapy treatment, if you don't talk about the Alancapin Faloxapin kind of combination. So, what use and what value is a listening discussion about mono therapy drugs for Bipolar I disorder when that is not where most of the treatment is going to take place. Clinicians need to have the capacity to use combination single therapy [unintelligible] what ever you want to call it (tape stops at 28.4) (tape 3 begins)

The studies the wind up in the literature that get accepted as evidence based, they have gone through the diagnostic rigor of meeting DSM for criteria so you know you've got apples in this group and you've got oranges in this group. But when you talk about the clinical practice in a community I really have concerns that that kind of diagnostic rigor does not exist. I cannot, you know while Jeff talks about a 1% incidence of Bipolar I and probably a 1% or greater incidence

of Bipolar II it seems to me that when I look at clinical records that I have to look at the number of, if we go to our data base and look at the DSM, the ICD9 codes for bipolar disorder it's huge. There can't be that many out in the community. And I don't know how to solve that issue in terms of there being an effort to get the diagnostic rigor.

Committee: That's the one I was trying to bring up to, when the PCP is diagnosing bipolar, much less going on to use these drugs [unintelligible]

Committee: So it is a difficult decision that you face in terms of, you, we, I, face in terms of trying to do the right thing. There really is a

Dr. Berlant: You have the right diagnosis to start and then you try to figure out which medicine to treat this, I like to just call it a mood disorder, that's my new term, my new favorite diagnosis is mood disorder and/or less, I love it. Because I'm not sure if I diagnose a three year old with bipolar disorder that's a life long condition that never goes away. It's not like he's going to out grow it like clothes. He can't out grow being moody. He cycles through depression. That's why I'm hearing reluctant to stamp a child, now adults may be slightly a little more spelled out. The DSM, Diagnostic and Statistical Manual does not spell out bipolar disorder in children it's just, if you try to apply adult standards to a kids, its just, even with a scientifically controlled study I don't know what criteria we would use to make the diagnosis, so. And the adult stuff is pretty nebulous. All the subtypes, Bipolar I, Bipolar II, and bipolar and all less Syothymea, [unintelligible] there a like about 6 or 7 different forms of it and so getting the diagnosis right is very important, then you've got to figure out which medicine to work, based on limited data.

One thing I would point out on this data or these conclusions they come to on comparative effectiveness, they do something here I don't think they've done in other reports and that is they only had two head to head trials of agent vs agent, I don't even know if any of those were in the comparative effectiveness, I know one of them was an adverse affect trial, I don't know where the other one was. So, they went and did this indirect which is really shaky and I don't think we have done that in any other report. I wonder if they did this on slights, I haven't gone back to the report; did they sort of analyze it this way in the report too? Is this just a reflection of the report or do they do this on the slights?

Committee: It pretty much follows the report.

Dr. Berlant: Yeah, that's my impression.

Committee: Cause that really shaky.

Dr. Berlant: It's one thing to do it on the safety side. That's very right Steve, in terms of the way it got cut.

Dr. Berlant: But I do put some emphasis on letters from providers in the community, Medicaid providers that there is support for Falotrtrin there too. We have to rely on people that are out there in the trenches that we have respect for the use of drugs.

Committee: I'm not really impressed with the evidence based information [unintelligible]

Dr. Berlant: I guess you've got to ask yourself, Are you going to try to change what psychiatrists do, probably not, because they know way more about this than anybody, you know, data is kind of interesting compared to other disease states. So then, do we have any sort of responsibility from private care practitioners with this new drug regarding their safety or at least what to think about when you pick one. To me Lamictal's a gimmick because its FDA approved for bipolar disorder. It's labeled for that use so, we can't say too much about it. For neurolpatic pain you probably could because its not, but. I just, If I was a primary care person in the state I would want to know out of these 20 drugs which are the top 5 if I have to treat this that I should even

have to think about first with no evidence to make those kinds of decisions, and maybe we can't. So, talking for Medicaid in a practical point of view what do we do with this information?

Committee: Would it be easier to do it as separate indications? Preferred agents for bipolar disorder, preferred agents for pain?

Dr. Berlant: We're talking about drugs whose main indication is epilepsy. And when the prescription gets entered at the pharmacy it's not entered for an indication, it's entered for a drug.

Committee: It's very difficult to restrict anything at that point.

Dr. Berlant: I'm not sure about that in terms of Kathy's concern about the Phil Peterson's out where they don't have ready access. I think we've got data that if he decides that he wants to use an anti epileptic drug we've got some data that would give him a couple of choices. We have no data on some of the new anti convulsants that are breaking the bank. And I personally feel that we have got to be responsible, as I said when we opened up this shop today, you know its tax payers money. How many people in this room are tax payers? My point is that we've got to draw a line somewhere. In the Medicaid system we don't quite have the luxury of, I mean, we've had it but there are going to be some drastic things that come down the pike that will affect the clinical arena, and we are here to guard that clinical efficacy point. So I think we do have an option to give Phil a couple of choices and say, Gee, if you want to prescribe other than these choices we've got to see some support for it.

Committee: Could you have exclusion with a history in the data bank? We've done that with previous ones, the diagnosis of the epileptic diagnosis that it could...

Committee: So, I guess what I'm asking is do you think that we can put some restrictions on these drugs?

Dr. Berlant: One issue that I have to is safety profile and side affect profile and the older medicines like Tegretal, Depraco, you know, I do really feel are less well tolerated than some of the newer ones. And I'm talking about if we tie into the blood draws checking for leucopenia and [unintelligible] disease, elevated transaminases and that to if we need to use stuff like Depraco, Tegretal [unintelligible] That's where the data is, but the reason as a practicing clinician I might choose to Tyleptal, Oxycabamazapin over Carbamazapin is that I don't want my patient exposed to blood draws three or four times a year, monitoring CVC levels and that kind of stuff. Plus I think the Oxycarbamazapin is better tolerated than Carbamazipin and I've clinically seen, you know, Oxycarbamazapin work just as well if not better. The safety profile of the newer meds. is something to be considered also for clinical efficacy. And I don't know what the costs are for Defco vs. Trileptel vs. Tegretal.

Committee: So it sounds like you're kind of going down the road of disease state these choices, I think that's one way the either way is to go by drug. This drug can be prescribed for this, this and this, because there is evidence behind the drug. In other words if you look at Nueronton and all of the off label uses do we restrict these Nueronton to those things that we have good evidence for.

Committee: But if somebody doesn't have an ICD-9 code already in place for, let's say they do have an ICD-9 code for bipolar disease and they come in with a prescription for Nueronton it would be rejected. Because you're saying there isn't good evidence for that.

Dr. Berlant: That's the way I'd like to see it work.

Committee: We've had other things where you've had to try other agents first and not even show that they failed, just that you've tried them.

Committee: And it's not your drug of choice it like... [Unintelligible]

Committee So which drugs, well which drugs, if we already have an approval for bipolar disease, let's say in this case, then we just say you have to have tried one that is approved already. We are talking about off label uses. So why not say, let's try an approved use one first.

Dr. Berlant Which for bipolar looks like shaky evidence follows that [unintelligible] they are the approved drugs they are the one's that have the best shaky data.

I don't know if we can comment on these other disorders because we were just going to look at neuropathic pain and bipolar unless we just say, those are the only two indications outside epilepsy for these medicines. Are we going to look at anxiety disorders, restless leg syndrome, plain old unipolar depression and...

Committee Are we being asked to make a judgment about that?

Committee No, just the two. And I would say about Rich the same caveat I gave about Jeff, which is an outlier when it comes to his practice he represents a class act as a child psychiatrist who many times, so and he is know in the community to access the more difficult cases. So, here is a bind that we're in, we want to cut the slack to the practitioners who we know render quality care we'd like not to give a blank check to the whole world for some of these drugs that are yet to be proved. They may all well be. Pick one of these that isn't yet a proven for, approved for the whatever, whatever we're talking about, Bipolar I, Bipolar II, Manic in the case of the Depracot use for the manic phases of Bipolar I. And that is something we have to struggle with and it may be something we just pass along to the administration. Gee, here's what we struggled with, here's what we think, that maybe it, that will be it, and the restrictions may have to come for financial reasons.

Committee Terry, I get the sense the committee agrees fully with that. I think it goes back to Tami's point though, this conversation, maybe we ought to initially look at it at the two disease states and how we would treat those. But then we are going to have to come to a decision, then how do you manage that.

Committee Well, I think it's from something else in the mix with the special and mental health issues we've got to look at folks that are stable on a medication. I don't know how many, like in Rich's practice, if we try the Trileptal then we get something saying this is not a per agent, you have to have tried something else.

I think we've done that before too where we grandfather it in.

We need to look at combinations. Like can they be on two or three anticonvulsants at the same time? For the same indication? What do you think?

Dr. Berlant I'm a purist, I use one in each class, unless it's and antidepressant sometimes you can get away with using a couple different types of antidepressants for other reasons, but I don't use to ADD's together to treat bipolar, I don't use two neuroptics together to treat, so

Committee And that's consistent with the guidelines where, there's no guideline that supports the use of two neuroleptics simultaneously except in a period of change over where you're going from one drug to another.

We need to take about five minutes to talk about neuropathic pain. So we need to go on from the bipolar disorder. Tami your point was do we do restriction relative to disease specific.

And to disease [unintelligible] guidelines or do we do drug guidelines?

Dr. Berlant Seems like you'll have to do drug because this prescription for Gavapen comes in, I mean, how are you going to be able tell them they should use Lamictal first if you don't even know they are using it for bipolar.

Committee Right, exactly.

So, you need to have, I would think you would need to go by the drug.

Dr. Berlant How accurate are their ICD-9 codes becoming? They are in the system already.

Committee Any of our prior authorization we have done, they are only as accurate as what goes in the system...

Dr. Berlant I know, but what I mean is, we've been doing a [unintelligible] of this a little for while now. So, how accurate are we already in having the right ICD-9 code.

Committee The right ICD-9 code is in there if it is given, if it is put in there. Majority of the time is that it has not been submitted and so that has to be submitted on paper.

That's still the way it is?

Yes. I mean if it's not put into the system there is no way we are going to pick up that ICD-9 code.

Well, you're certainly not going to pick it up from the drugs.

Just a note about ICD-9 codes they are required, the primary care guy, if I need an MRI they bring me the ICD-9 code and I look through to find what is closed, if mine doesn't if they need it, so if we're going to be limiting access by ICD-9 codes the ICD-9 codes are going to change to fit what they want to prescribe.

And we note that. That happens.

I think in your case you're talking about a sort of subtle gray area. Changing from bipolar, oh no, they've got epilepsy now.

You know we get that with ADHD when we know they are not using stimulant for ADHD. They are using the stimulant for something else.

So, Steve's point of being drug specific, we can go with that?

I think we can.

Are we going to go through each drug now?

I don't think this discussion needs to go that way, you know if we had to pick and choose for bipolar disorder which drugs you'd want available, which ones would you want to make sure you had available.

Rich has made his pitch.

I really think we need to pick the ones that have got approvals already. You know that should be the first line therapy. We need to have those approved that they can use approved drugs already.

Dr. Berlant I think it reflects what clinical practitioners would do anyway and that's you know Lithium which is not the topic right now [unintelligible] acid and maybe Lamictol. So why aren't we using more Lithium?

Committee Well, we're not here to talk about that. We're here to talk about these drugs.

But could we say you need to try that first?

I don't think we have evidence to say that.

That's not been looked at because...

So we need to look at it...

Dr. Berlant Lithium comes out of the ground with no profitability to it. I apologize for sometimes being blunt, but there practical things that we might a well put on the table. We live in a capitalistic society and we're going to work within that system to the best that we can. OK. Kathy.

Committee So, when I was reading the report, I actually read most of this report, I don't really even like psych, but I thought I was learning something, on the second page is kind of our out on this I think because it says, I forgot about this, American Psychiatric Association and the British Association of Psychopharmacology both recommend Carbamazapin, Malotragene, Oxcarbamazapin and Valproic acid for acute maintenance phase if bipolar disorder. That's just one part.

I think this gets to the bulk of what these agents are used for. It's add on therapy for bipolar disorder whether it's acute or chronic.

So, I need a recommendation.

I would like to ask Rich how strongly do you feel about adding Oxcarbon as a...to that

? It's my number one, as a child psychiatrist...

Committee Do we see any data about Tegratal in bipolar? Is there...

? Yeah.

They weren't always good studies. And there's more with that than with the newer drug but...

Committee Neuropathic Pain.

Dr. Berlant You know, you don't want to lock into this one to tightly because there is that new drug coming. We sincerely hope it will be better than what we have. That's the challenge for the pharmaceutical industry is to make the next one better than the last one. The problem is showing for a longer period of time than the three month it hits the market that is necessarily going to shown to be safe and effective. Alright. Clearly then we have an indication for post herpetic neuralgia. What do you want to suggest consider other uses for this class of drugs? Whether...

Committee [Unintelligible] That was I think on the diabetic side wasn't it? Yeah, and Proet also had fair study. Not impressed with the Lamotragene data.

Can you make, are the [unintelligible] close enough that we can just call it a pain diagnosis rather than...

No, it's...

So, we'll have to pick the big ones?

Well, I, if that's the decision that the committee recommends then we would come back with criteria.

Satisfied with that?

Let's take a 15 minute break before we have the presentation.

Dr. Berlant May I ask one more question?

Committee Yes, go ahead.

Dr. Berlant Can I go back to bipolar? So, for the psychiatrists, they will have probably already tried some of the stuff on our first [unintelligible] list right, anyway? They will be down into some of the other drugs that [unintelligible]. Every drug is available...but you just want to make sure for the specialists that end up with referrals that that works ok, right?

Committee Yes, we have to structure it some how.

Dr. Berlant Well, we come to you and they have tried everything else except for the one that's approved for already, you're going to be hearing, we hear there's a new medicine that is coming out tomorrow and we've been on everything else.

Committee We have, and this is something to consider we have on some drugs if we can pull out the specialty like our Antiemetics if the physician is an oncologist then...

I was asking you to do that with this and you said how about [unintelligible]

It depends on the specialty.

Those are logistic problems that will be administratively responsive. Administration will have the responsibility for working that out. I think what you've done, you've taken the best judgment you could get relative to which agents there's significant support for making these recommendations, how it gets worked out, poor Tami and the rest of the pharmacy will have to struggle with.

Fifteen minutes, we'll be back here, let's take 10 minutes, let's do that. We're a little bit off schedule here.

And receive dollars that wouldn't be allocated if it was just another company who was putting in a private free standing facility. So you're talking the same beds, the same level of care and so on, the difference is that if they are attached to hospital then they automatically going to get this higher rate if they go into the hospital [unintelligible]. That's what I'm saying any new providers from here on out, any new people would then go right into the urban or free standing array.

I think I can live with that. Kevin is that consistent with what you were talking about?

Well, I don't see why it wouldn't be. What Kevin is saying, and I agree with him, is that, ok, we establish one array; we have the hospital based...

OK, I understand. I wanted Kevin to answer.

OK.

I understand what you're saying about having it as one array but what about the new providers that come on? How are they treated?

Well, I

Which percentage are they given...

I think you are going to presumably end up with this same deal that apparently you didn't want. It's easy to write a rule that punishes somebody that doesn't exist yet. No one is there saying, this is a bad thing. Two, three, four, five, ten, fifteen years from now there's a handful of these guys that this rule that was written way back when, actually starts to punish and then you've got to stand up and say why I did that. Why I think it's fair. And if you can do that now...

I think I am asking a simpler question than that. All I'm saying is, how will you treat, how are you proposing under what you were proposing to treat new providers that come in? Would a new hospital based provider have the free standing percentage or would they...

I was probably more in DeeAnn's camp on that. I think you've got the two pools and they have to fit into one of them. If they are a hospital based provider that meets the other criteria, they get in that pool.

So you've given up your idea of phasing out the difference.

Well, no, I think you could still do that but if I was going to do that I do it to everybody that fit into that pool. What we're saying is we like the idea of phasing it out but only for the brand new guys.

And would the time run with the individual provider? I mean it's a ten year phase out depending on when you can in?

No, I think the clock would start and we're going to add another 10% on to the limit this year.

So, after 10 years everybody coming in (tape ends)

Dr. Berlant

The clinician needs to have the flexibility to have at their reach the tools that may stabilize them. This is not only true of Lithium, Valproic Acid and Lamotragene but also other drugs that are showing great promise like Oxycarbamazapin, Kepra. These other anticonvulsants also seem to be useful in at least a subset of patients. Although it sounds expensive some of these patients need three or four mood stabilizers to get control. But compared to the high cost of poorly treated bipolar patients it's a drop in the bucket. So, I do hope that as you look at this you'll see that the type of medethenolisis that the DUR project has done is not suitable for answering the questions that you need to answer. You know they say that doing a medethenolisis is easy. Doing a good medethenolisis is hard. And that is not a good medethenolisis for our purposes. We have lots of holes in our database many of the pivotal questions that we need to have answered are not answered. But because there may be a lack of those studies done I would be very cautious about having this committee narrow choices in terms of being able to treat. Were am I going with this? My recommendation is to make all of the antiepileptic drugs available for the use of bipolar disorder patients. Because I think other than to do that is to create a very high burden on unanticipated cost of hospitalization. We can see where treatment resistant patient is hospitalized but under the Medicaid formulary the physician is not allowed to use an agent that is not on the formulary and the patient goes untreated and unstablized. That is not good clinical care; it's not good managing of resources.

Committee

Dr. Berlant, we have about two minutes. If there's a chance to give some feedback.

- Dr. Berlant That I think is my point and I hope that these points do lead to the use of your best judgment in giving clinicians enough opportunities and flexibility to treat the very ill patients that they may have.
- Committee OK, I'd like, take a couple of minutes for questions because Jeff has obviously made some points that do represent a challenge for us to struggle with.
- Steve Montamet Jeff, Steve Montamet, I just want to ask, How do you feel about the value of clinical trials in psychiatric medicine as compared to when we're looking at diabetics or coronary disease and looking at outcomes because I do take your point about the DUR report but a lot of it is just data gathering and trying to find, trying to collate what data is out there, we have to take what their recommendations are with a grain of salt especially when the evidence out there is pretty poor. None the less, in most areas of medicine I like to know what the evidence is and I want to see that evidence about how a drug works and how safe it is. Can you comment to that in psychiatry?
- Committee Having clinical trials, having evidence is extremely valuable. Misusing it is where the problem comes in. There is one fundamental difference between these clinical trials and many say clinical trial for treatment of [unintelligible]. That is a specific biological entity. We do not yet have the technical capacity to identify the biological lesions that lead to these behavioral syndromes. These are real syndromes. They are based somewhere in altered biology. But we don't have the ability, yet, to pinpoint it. So that degree, psychiatry is at a disadvantage that the trials are less specific to a problem that is just a heterogenetic and clinician unfortunately just have to struggle with finding the agent or combinations of agents that [unintelligible]. Sometimes in individual cases we don't find it.
- Steve Montamet And it I could, that would lead me to a second question. And that is what do you believe is the ability of primary care physicians to both diagnose and treat disorders such as bipolar disorder with the advent of pretty safe antidepressants primary care has become more comfortable with treating these kinds of conditions and you even mentioned in the last 5 to 10 years there are new agents that, off label use, I don't know that primary care physicians unless they really focus on that disease entity, how do you feel about that?
- Committee Well, I can envision situations like in rural practice where there are no specialists. Having a primary physician do they're best is all they can do. And I think the tools are better and using linkages with consultants can help. Those of us who have a specialty practice; we have to struggle with these patients to find good solutions. It is very time intensive, requires a lot of contact with the patient. It sort of goes against the grain for what the primary care practices are constructing. So, generally my feeling is unless there is a primary care doctor who has a particular interest and experience with it, they are unlikely to get the feel of how to handle it. It's hard enough for many psychiatrists to handle [unintelligible] and I'm not even going to get into the controversy about antidepressants.
- Other questions? Kathy.
- So, I'm a pharmacist not a physician but would it be fair for the primary care providers in the state to have every single anticonvulsant available for bipolar disease verses pick like the three or four best ones that those people that they had to could start with maybe the safest ones before you gave that person to a psychiatrist if they failed because I understand there are a lot of people that your going to have to go through many drugs to get to the right thing and you may have to have a combination of drugs.
- ? I think you need some kind of system where it is fine to educate physicians or psychiatrists or whoever is taking care of these patients, about these seem to be the most promising drugs and you should probably use these first and then we have second line for [unintelligible] concussions. I guess what I am trying to argue against is the use of a closed formulary and more

in favor of educating psychiatrist about the most cost effective way to approach these. A few studies done in other areas looking at cost effectiveness find that the least cost effective, in fact counter productive strategy, is a closed restricted formulary. Where as physician education is the most effective [unintelligible] at lowering an over all cost of care. So I don't know exactly how that would be translated but some model of that sort which provides education and yet [unintelligible] access to all of the agents as needed is going to help. Particularly patients who don't respond to the Lithium, Valproic Acid, Lamotragene who need to have access to the more speculative treatments. Those are low cost compared to the cost of remaining chronically non-responsive.

Committee

Let me just toss in a couple of things to wind it up and Jeff we do appreciate the challenge you've thrown out. I would like to answer in my one time of participating in the evidence based practice center there at OHSU. The two physicians, John Santos and Mark Halfant, are very, very good internists and bring to the table a lot of clinical experience. I realize from the psychiatry stand point, both when we had the antidepressants at our November meeting and the Chapel Hill people they use psychiatrists in putting that together. We'll see the same thing when the atypicals come up in March. Second thing I would like to say is I believe when you quote the most effective tool being the education arm, where those thing have been shown have been in situations where physicians share risk for the cost of care. That doesn't happen in Idaho except for maybe as much as 10%. Physicians who don't have to share risk of the cost of care are uneducable because they are loose canons. Now I know that's a grandious statement, it's painting a picture that is a broad brush accusation to everybody. But having worked on the payer's side as long as I have it does appear to me that unless a physician has some chance at having to take a look at the cost of care, education is a waste of time. It ends up in the round file because it won't change the behavior. But I hear you loud and clear. You're absolutely right. If we had a way in this state where physicians had to be at least cost conscience and I don't think it happens or it happens in much small circumstances. And I think the other thing the panel needs to know about Dr. Berlant, I have the highest regard for him, his remarks I have to take a little bit with the bias that he brings. This is the guy who treats the untreatable. So, he feels very strongly about the need to have access. This is not the kind of practitioner who is going to abuse the privilege of, as he used the word polypharmacy. Hearing it come from Jeff, it doesn't have quite the pain as it would hearing it from somebody else because I know he's concensus, I know he's got the most difficult cases. Jeff, thank you for taking the time to come.

Thank you for allowing me to share the dilemma with you. Thank you. Thank you for the kind words.

And, Dr. Patel.

Sneha Patel, PharmD, Wyeth. – ACE Inhibitors

Dr. Patel:

Good Morning. My name is Sneha Patel and I am a PharmD with Wyeth Pharmaceuticals and their Global One Affairs Department. And I would like to begin by thanking the committee members for giving me the opportunity to provide comments on Altace. Altace is the only ace inhibitor that is approved by the FDA to reduce the risk of stroke, MI and [unintelligible] in high risk patients 55 years of age or older. This indication is based upon the robust results of the Hope Trial, which demonstrated that Ramapril significantly reduced the primary composite M point which was stroke, MI [unintelligible] in high risk patients 55 years of age or older. In addition, Ramapril also significantly reduced the risk of each of the individual M points of stroke, MI and [unintelligible]. Of each of these individual M points were also primary M points and the secondary M point of total mortality was also significantly reduced by Ramapril in the

Hope Trial. Now, it is important to know that the benefits observed in the Hope Trial were seen among patients who were already receiving standard risk reducing therapies such as aspirin, beta blockers and lipid lowering therapies. Being that the benefit was independent of the blood pressure reducing affect as all patients had control of blood pressure at base line and the mean reduction in blood pressure with treatment was extremely small. The micro Hope study which was a pre-specified sub study of the Hope study, evaluated whether Ramapril improved the CD risk reduction in diabetic patients who had at least one other cardiovascular risk factor. In this study, Ramapril significantly reduced both the primary composite M point in each of the individual M point of stroke, MI and [unintelligible] in diabetic patients. In terms of comparing ace inhibitors we have no head to head trials; however there have been two observational studies that did compare them. The first was a prospective multi-center registry of over 14,000 patients who ST elevation myocardial infarction. This study demonstrated that Ramapril was independently associated with a significantly lower hospital mortality in the lower rate of non - fatal major adverse coronary and cerebral vascular events compared to other ace inhibitors. The [unintelligible] was a retrospective cohort study based off of hospital discharges and prescription data bases in over 18,000 patients who are at least 65 years of age or older and who are admitted for an acute MI. This study demonstrated that the mortality rate in the first year after an acute MI was significantly lower for patients receiving Ramapril when compared to patients receiving Analapril, Captapril, Quinapril and Fasinapril. The cost effectiveness of Altace has also been reported in several studies based off the Hope data in terms of safety like all ace inhibitors Ramapril has a black box warning for use in pregnancy and the common adverse event of the flu, cough, dizziness, symptomatic hypertension. There have also been rare cases of anjuadema that have been reported. So, in conclusion the robustness of the Hope and Micro Hope trial have not been duplicated by any other major ace inhibitor outcomes trial. In fact, other ace inhibitor outcomes trials may have shown a reduction in the primary composite M point, but none of them showed a reduction in each of the individual M points except for non fatal MI. And just to reiterate, Ramapril in the Hope Trial significantly reduced both the primary composite M point in each of the individual M points of stroke, MI and CB[unintelligible]. I would like to thank you and ask if there are any questions.

Committee

Thank you Dr. Patel. Questions? Thank you again. I think we are at a point where we can break for lunch. That will give us a longer break period. We are scheduled to reconvene at 12:45; we'll have our discussion and clinical conclusions relating to the selected therapeutic classes at that time. Thank you. Adjourned.

Let's talk about the ace inhibitors. Is that agreeable?

Yep, sounds great.

What did we decide last time?

I don't have the list with me. I know we went with generics.

But the really decision was though based on that they were about the same. There wasn't any huge difference. Although there a specific indications.

But I don't know if we made any limitations based on diagnosis.

No, we didn't do like we did with the beta blockers.

So, I guess the decision is...

Is there any new data to suggest that we change? That would be the quickest, easiest way.

That was the conclusion in the data we were given in our review, that there is no new data to change our minds.

I guess what we ought to do is review what the actual decision was the last time.

Mary, do you know which drugs we actually chose?

I can get if for you, it's on the website.

I have it right here.

I was waiting for the slides to come up. So, let's, who wants to be the person of attention in terms of a discussion?

As far as we can remember the drugs were Ramapril, Analipril and Mycimapril. And the question is, is the data from the Hope study, do we believe that that is specific to Ramapril or is it a class affect?

Well I don't think there's anything new since our last review. I think what was our question last time was we don't know if its class affect and certainly Ramapril has the evidence.

And the net affect is nil relative to where we stand as we are currently operating. Doesn't change anything.

I think the preferred agents are everything. Just in their generic forms.

Not having been here in July I leave it to those of you who participated in that to compare where we are today verses where you were then when you made that decision.

I guess, you know, this decision was made after considerations... maybe we could have a summary of what we thought during the discussion period before we look at rebates and so forth, because I think that is what we want to do here in this discussion right now.

Well, this is the recommendations that [unintelligible]. I think we said we should leave it up to the practitioners to be able to choose.

That language is also reflected in the minutes.

What I would like for this discussion to be around would be the clinical aspects without necessarily discussing rebate. That can be taken into consideration during the time that we have closed sessions. I want to try to stay focused just on the clinical piece of this.

Other than the Altace question I think to me they look pretty similar as long as individually you have two or three to choose from.

So would you recommend including the Ramapril as one plus two others?

No. I guess in my opinion it would be nice to have it in there if, but then that would be a cost choice too.

Clinically I have to agree with you. There is some evidence that it's perhaps better, we should have it available.

I don't think there is evidence that it is better. It has evidence that it is...

Equivalent.

Yeah.

The pharmaceutical representative testified to us that the Altace and [unintelligible] both had demonstrated that the others had failed. Implied or half way stated that the others had attempted and failed. But I didn't see that in any of our stuff.

Where's that dated?

Right on the top.

I think it gets down to whether there is lack of evidence for the others or whether evidence that shows that they're inferior.

They just haven't done the studies.

Right, exactly.

The other thing and this wasn't brought out but I've heard the [unintelligible] is the dose used whether that is Ramapril at 2 mg. equivalent to a lower dose.

1.25 didn't work.

It was a different indication population too.

That would mean the committee's thoughts from the clinical side would be that there is no data in the re-review that would alter the decision previously made as to how our preferred drug list is working.

Alright, any other discussion relative to ace inhibitors? Let's talk about the AED's. Antiepileptic drugs.

Based on the evidence reading through this, the only thing I really see in this data that Nerontangetapentan is probably not very affective, there are some studies that show it is less effective than placebo treating bipolar. I get we've talking about mainly hypomania. And there is some good data that Lamotragene is as effective or more effective than the older drugs that we use like Lithium and Tegretal. So I'm disappointed there is not more data on the other entries like Tobamax, Oxycarbamazapin, Trileptil, even [unintelligible]. So I just think there is so little data here it is hard to make any decisions based on the evidence for Zomag except those two comments about Neurontan and Lamictal.

So, how do they get into clinical practice if they're, excluding psychiatrist and people who do this for a living and read the literature and go to the meetings and see the case reports? The primary care people, how do they start using one of these antiepileptics?

I think the psychiatric community takes the lead. There is data coming out that a lot of these anticonvulsant medications are helpful in treating bipolar mania, hypo mania, depression. We figure if one works, we know that they all [unintelligible] they figure that maybe the other ones might work as well. So they jump on the band wagon. And some have been found to be more helpful and others haven't like traditionally Dilanton is not been very helpful in treating bipolar disorder. We initially thought Neurontan was going to be helpful and it has just kind of fallen by the wayside. Now we're looking at it more for anxiety disorders. Had better clinical experiences like Trileptal and even Topeamax to some degree. I'm not as up on Lamictal question as I treat kids and I'm just real cautious with using it because of the Stevens Johnstons syndrome effect in children. I have about three Mamictal. I know my adult [unintelligible]. I see that prescribed a lot. So, I think just because the drug class works for one they... a lot of these medicines have been affective in treating mood disorders.

Dr. Pines, is there a source of information or is there some literature out there in the psychiatric community that's not affected by this? That is not picked up by this?

All [unintelligible] case reports. When I read what's our bible, the green journal and the orange journal, the child and the adult forms of our, we get a lot of our claims information, doctors are writing about, gosh, I tried this and I had three patients that did well, they are not scientifically controlled studies, this worked, this seems to do well, and then you read a couple and say hey, maybe I will try that. And I do those a lot of times when these antiepileptic drugs come out in the pharmaceutical [unintelligible] even before the FDA [unintelligible] samples available, try them. If they have a couple of good experiences then you write into the orange journal and say I had five kids on Trileptal and it really seems to work for the irritability in mood disorders. Half the time I don't even know if I'm treating bipolar disorder in kids. Irritability and mood problems, even making that diagnosis in a child is extremely complicated.

Being asked to make these decisions on evidence based material not antidotal material.

So that's why I'm saying all I can get out of this data today is those [unintelligible] points. There is not enough information; maybe Neurontin isn't as good for treating bipolar as we thought originally and there's some [unintelligible] of Lamictal may be better than some of the older drugs that we're using. Or as good with maybe different risks or lower risks. And I sort of already knew that. If you were asking before I looked at any of that what I thought, that/s what I would have thought.

I think that that is there relative to Depraco.

Depraco and Segratol the two of them we've kind of known for years. Have their risks but are affective in treating certain forms of bipolar disorders as well as Lithium.

I'm talking about the newer agents like Topamax [unintelligible]

I see one of the problems in terms of like Dr. Berlant pointing out the discrepancy in the actual clinical arena where the physicians are having face to face contact verses looking at published data. One of the problems I think is that there is not the diagnostic rigor in the general office setting just like Rich said in terms of the difficulty in sorting out, does this child actually have bipolar (tape ends)